Efficacy of Therapies Targeted at Treating Patients with Membranous Glomerulonephritis

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Membranous glomerulonephritis (MGN) is the most prevalent underlying cause of nephrotic syndrome in adults. Previous studies have uncovered numerous mechanisms by which MGN progresses to end-stage renal disease (ESRD), which could spur the development of therapeutic strategies. Definitive courses of treatment, however, have yet to be established.

In order to test the hypothesis that the combination of mycophenolate mofetil (MMF) and angiotensin-converting enzyme inhibitors (ACEi) results in significantly slower rates of progression to ESRD, we analyzed data from randomized clinical trials via the Pubmed database. Studies that evaluated the effects of MMF, ACEi, cyclophosphamide, corticosteroids and other medications or combinations thereof were also included. The objective of this study is to compare MMF plus ACEi to cyclophosphamide with regard to the endpoint of rate of progression to ESRD (defined by a creatinine clearance of less than or equal to 10). Disease remission rates suggest similar performance for the medication combinations studied, without significant statistical difference in efficacy. The combination of MMF with ACEi, however, elicited a 33.3% failure rate. Cyclophosphamide proved most effective with respect to complete remission rates (78.6%); the next most effective treatment was MMF (60%). These results indicate that cyclophosphamide monotherapy could become the primary option in treating MGN. Given its potentially dangerous side effects, however, large prospective, randomized, placebo-controlled trials would be needed to confirm these findings.

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Introduction

Membranous glomerulonephritis (MGN) is the most prevalent cause of nephrotic syndrome in adults, and remains the second most common cause of end-stage renal disease (ESRD) in the world.[1] The exact pathogenesis of this disease is unknown, though the disease is characterized by proteinuria and thickening of the glomerular basement membrane. Despite advances in medical technology and research, approximately one third of patients afflicted with MGN still progress to ESRD after eight years.[1]

The variability of its natural history, often manifesting in spontaneous remissions and relapses, has spawned a controversy regarding the best choice of treatment.[2] Although most researchers agree with using immunosuppressive agents, the efficacy and side effects of these and other drugs remain an unresolved issue.[1] Nevertheless, recent evidence suggests that the immunosuppressant, mycophenolate mofetil (MMF), combined with either angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II type 1 receptor blockers (ARB) could become a frontline therapy for MGN.[3] Their roles in preventing organ transplant rejection and lowering blood pressure respectively are already well-documented; it has been speculated that simultaneously inhibiting the glomerular basement membrane inflammation and restoring blood flow to the kidneys could hold the key toward successfully treating this disorder.[3] We performed a meta-analysis of randomized clinical trails on MGN therapy in order to test the hypothesis that the combination of MMF and ACEi or ARB results in significantly slower rates of progression to ESRD.

Methods

We utilized the Medline and Pubmed databases to screen for clinical trials from 1979 to present relevant to the treatment of MGN. First priority was given to studies that enrolled patients with MGN. Articles involving treatments for other forms of glomerulonephritis were also considered for comparison. Upon reviewing each study, we extracted and pooled the data, first according to treatment and then into three commonly used indicators for glomerular diseases: proteinuria (g/24h), serum creatinine (SCr; mg/dL) and total remission rates, defined as the sum of complete and incomplete remission rates.

Meta-analysis was performed using the GraphPad Prism Version 2.0 software, which calculated *P* values utilizing Fisher's exact test or the chi-square test, as well as relative risk (RR). The difference between treatments regarding proteinuria was analyzed using unpaired Student's *t* tests. A *P* value of less than .05 was considered significant.

Data Analysis

In all, 37 studies for proteinuria and 34 studies for total remission rates from 2515 patients (1268 proteinuria, 1591 total remission rates) were analyzed (Tables 1 and 2). Compared to placebo, the RR (chance of no remission) of the medications was 0.2149 for cyclophosphamide/corticosteroids (ie, a patient treated with that particular combination has a 21.49% chance of experiencing no remission as one treated with placebo),

Table 1. Patients with total remission (TR) vs patients with no remission (NR)

Treatment	Patients with TR	Patients with NR
Cyclophosphamide + corticosteroids	366	63
Corticosteroids	403	86
MMF + corticosteroids	88	33
Chlorambucil	117	58
Cyclosporine A	107	99
Placebo	38	82

Table 2. Mean percentage of patients with a decrease in proteinuria after treatment

Treatment	Number of Patients	% Decrease in Proteinuria
Cyclophosphamide + corticosteroids	116	78.82 ± 1.36
Chlorambucil	105	73.72 ± 4.84
Cyclosporine A	107	68.73 ± 7.41
Corticosteroids	151	65.08 ± 6.11
ACEi + ARB	95	44.88 ± 11.72
MMF + ACEi	53	38.07 ± 13.83
ACEi	345	36.63 ± 4.07
ARB	76	34.21 ± 3.54
Placebo	237	24.00 ± 8.95

0.2574 for corticosteroids, 0.3991 for MMF/corticosteroids, 0.4850 for chlorambucil and 0.7033 for cyclosporine A. Moreover, when compared to cyclophosphamide/corticosteroids, the RR was 1.035 for corticosteroids, 1.173 for MMF/corticosteroids, 1.276 for chlorambucil, and 1.643 for cyclosporine A. Table 2 shows the percentage of patients with a decrease in proteinuria for each medication. However, serum creatinine could not be analyzed due to the lack of this information in the studies reviewed and analyzed.

RESULTS

The combination of cyclophosphamide and corticosteroids performed better than other medications except corticosteroids (P=.2446) with respect to total remission rates (85.86 ± 3.19%). Indeed, while the corticosteroid group was not far behind with a 70.64 ± 5.76% total remission rate, the large standard deviation (SD; 15.25%) relative to that of cyclophosphamide/corticosteroids indicates considerable variation of data among this group of patients. MMF and corticosteroids (P=.0026), cyclosporine A (P<.0001), and chlorambucil (P<.0001), while not matching the cyclophosphamide/corticosteroid therapy in efficacy, presented significant/better outcomes than placebo (Figure 1).

In terms of proteinuria, the cyclophosphamide/corticosteroid therapy appears to outperform the other medications (78.82 ± 1.36% decrease), although such results were not significantly different from cyclosporine A (P=.2171), chlorambucil (P=.3766), or corticosteroids (P=.0593). It is interesting to note that MMF/ACEi, ACEi, ACEi/ARB, and ARB were not significantly different from placebo in this respect (Figure 2). This revelation is surprising, especially considering the widespread uses of ACEi and ARB to treat proteinuria. Given the large amount of data already available on these drugs, these results suggest that the renin-angiotensin system or the purine pathway (MMF) might not be as crucial to the pathogenesis of MGN as most researchers are inclined to believe, and that future research might be better served focusing on the inhibition of other pathways.

CONCLUSION

We conducted a meta-analysis of clinical trials of drugs aimed to treat MGN in order to consolidate existing knowledge about MGN therapy and examine if the MMF/ACEi combination

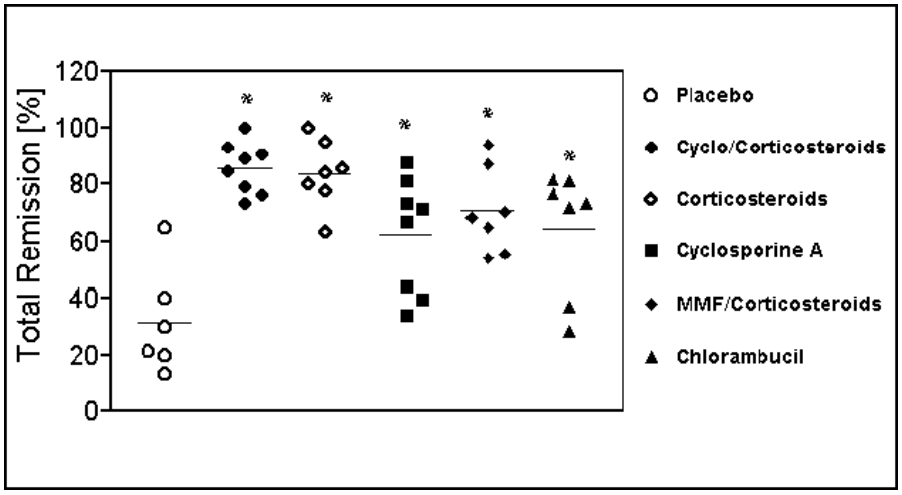

Fig 1. Total remission rate in MGN patients after treatment *P<.001 vs. placebo

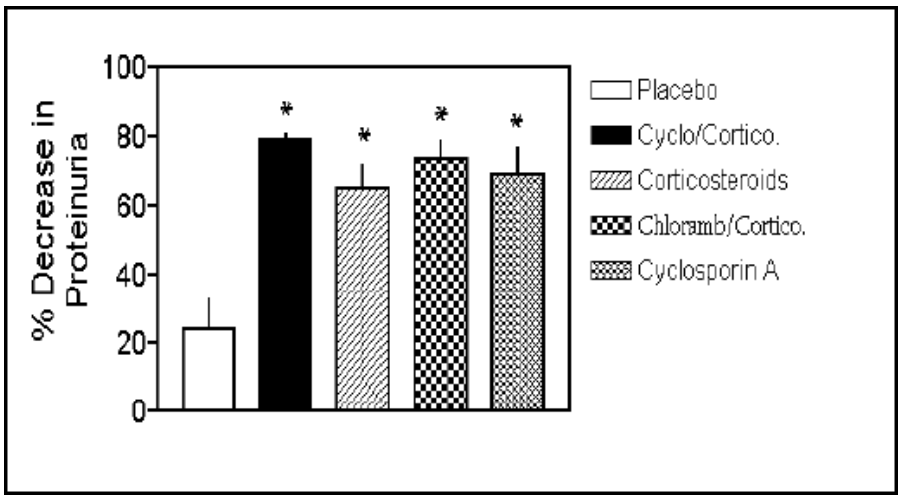

Fig 2. Percentage of patients with a decrease in proteinuria after treatment. *P<.01 vs. placebo

could be as potent as recent studies have suggested. After analyzing data on proteinuria and total remission rates from 2515 patients, we found that cyclophosphamide/corticosteroids represent the most effective treatment to date for MGN, and that the MMF/ACEi combination was not as effective as hypothesized. However, the documented side effects for all medications are considerable, ranging from leukopenia to increased risk of infections commonly associated with immunosuppressive regimens.[4-5] Therefore, both the efficacy and side effects of these drugs must be taken into account if they are to be administered as a front-line therapy for MGN in the future.

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